

Tuberous Sclerosis Complex in Autism

Xin Guo*¹, MD; Wen-Jun Tu², MD, and Xiao-Dong Shi², MD

1. Department of Clinical laboratory, The First Affiliated Hospital of Harbin Medical University, Harbin, China
2. Department of Clinical laboratory, China Rehabilitation Research Center, Beijing, China

Received: Jul 09, 2011; Final Revision: Feb 25, 2012; Accepted: Mar 05, 2012

Abstract

Objective: To study the prevalence rate of tuberous sclerosis complex in autistic disorder.

Methods: We studied one cohort of children followed up since 2005 until 2009, with autistic disorder, to determine the incidence of tuberous sclerosis complex. We established an autistic disorder registry in 2005 at China Rehabilitation Research Center. During the 4-year period (2005–2009), we collected a database of 429 children (390 boys and 39 girls; male to female ratio 10:1) with autistic disorder and pervasive developmental disorders. We routinely examined all children with autistic disorder for any features of tuberous sclerosis complex by looking for neurocutaneous markers such as depigmented spots. In those with infantile spasm or epilepsy, the clinical features of tuberous sclerosis complex were monitored regularly during follow-up.

Findings: Of these, five had tuberous sclerosis complex. Thus, the prevalence rate of tuberous sclerosis complex in autistic disorder is 1.17%. All of these children were mentally retarded with moderate to severe grades. Their IQ or developmental quotient was less than 70.

Conclusion: The prevalence rate of tuberous sclerosis complex in autistic disorder was 1.17% in our region; autism spectrum disorder is a condition that might be associated with development of tuberous sclerosis complex.

Iranian Journal of Pediatrics, Volume 22 (Number 3), September 2012, Pages: 408-411

Key Words: Tuberous Sclerosis Complex; Autism; Autistic Disorder; Neurocutaneous Syndromes

Introduction

Autism is a neurodevelopmental disorder characterized by a pattern of social and communication deficits. Recent data have provided convincing evidence for multiple interacting genetic factors as the main causative determinants of autism^[1]. Tuberous sclerosis complex (TSC) is an autosomal dominant hamartomatosis with multisystem involvement

including the brain, skin, heart, and kidney. The disease is characterized by a broad physical phenotypic spectrum with epilepsy, mental retardation, renal dysfunction, and dermatologic abnormalities. TSC is caused by a mutation in the *TSC1* or *TSC2* gene. If autism and TSC were independently occurring disorders, it was unlikely to identify many patients with both diseases, given the individual prevalence rates of 1/110^[2] and 1/6000^[3]. The basis for this association is not well

* Corresponding Author;

Address: No.23 You Zheng St., Harbin City, Heilongjiang Province, P. R. China 150001

E-mail: zsf0508@163.com

understood, although elucidation of the mechanisms would throw light on the brain basis of idiopathic autism where there is strong evidence for a genetically determined neurobiological abnormality, but little understanding of its nature. Awareness of the relationship between autism spectrum disorder and tuberous sclerosis complex is important during the evaluation of individuals with either disorder. Many authors have reported the relationship between Tuberous Sclerosis Complex and Autistic Disorder. Unfortunately, most of the published research has come from Western industrialized countries^[1-4]. We report on a cohort of children with autism, to determine the prevalence rate of tuberous sclerosis complex in autistic disorder in our region.

Subjects and Methods

We established an autistic disorder registry in 2005 at China Rehabilitation Research Center. All patients in this study came from this registry between June 1, 2005, and May 31, 2009. All the patients who were eligible to participate in this study had to have the typical triad of symptoms of autism: social deficits, communication impairment, and rigid ritualistic interests. Diagnosis of autism spectrum disorder was based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders-IV^[5] and the Autistic Disorder Diagnostic Interview-Revised^[6]. In all children with autistic disorder, we routinely examined for any features of tuberous sclerosis complex by looking for neurocutaneous markers such as depigmented spots. In those with infantile spasm or epilepsy, the clinical features of tuberous sclerosis complex were monitored regularly during follow-up. We adopted the 1999 diagnostic criteria of tuberous sclerosis complex for case ascertainment^[7]. Cases were ascertained by one of us (Wen-Jun Tu) during the course of study. Estimates of the children's abilities were made using standardized cognitive tests appropriate for age and/or ability (Mullens scales, the Wechsler scales, the Ravens Coloured Matrices and the

British Picture Vocabulary Scale). Unfortunately, none of the cases had genetic analysis because genetic analysis for tuberous sclerosis complex is not available in Beijing. A low mental age was seen as an exclusion criterion as it precluded confident diagnosis of an autism spectrum disorder and parents had poor compliance for following up in this study.

The details of the study were explained to the parents of the participating children, and written informed consent was obtained from the parents.

Statistical analyses were performed using SPSS version 17.0 (SPSS Inc, USA) for Windows (Microsoft Corporation USA). Continuous variables are presented as mean \pm SD. Qualitative data were expressed as percentages.

Findings

During the 4-year period (2005–2009), 632 patients were admitted to our center. We collected a database of 429 children (390 boys and 39 girls; male to female ratio 10:1) with autistic disorder and pervasive developmental disorders. The rate of participation was 67.9%. The mean age was 5.2 \pm 3.1 years. Of these, only 4 cases were non-Chinese, one was American, one was Korean, and two were Europeans. Demographic characteristics of the patients are summarized in Table 1.

We routinely examined all children with autistic disorder or pervasive developmental disorders for any features of tuberous sclerosis complex by looking for neurocutaneous markers, such as depigmented spots, which appear in 43% of children with tuberous sclerosis complex by the age of 30 months. Of these, five had tuberous sclerosis complex. Thus, the prevalence rate of tuberous sclerosis complex in autistic disorder was 1.17%. The mean age was 3.6 \pm 2.1 years. All of these children were mentally retarded. Their IQ or developmental quotient was less than 70 (49 \pm 13). Only one of them had a positive family history. Four out of the five TSC patients had bilateral lesions, while 23 of the 424 non-TSC patients had temporal lobe lesions

Table1: Demographic characteristics of the autistic and TSC patients

Parameter	Autistic patients n= 429	TSC patients n=5
Sex (M/F), n/n	390/39	4/1
Han race, (n)	425	5
Age [mean (SD) years]	5.2 (3.1)	3.6 (2.1)
Family history of TSC, n (%)	2 (0.47)	1 (20)
IQ [mean (SD)]	54 (16)	49 (13)

SD: Standard Deviation

Discussion

Our China Rehabilitation Research Center receives referrals from mainland of china for children with developmental problems such as autistic and speech delay as young as 4 months. Thus, our registry for any disorder, such as autistic disorder and pervasive developmental disorders, can only represent the profile within a single region. Furthermore, this was a hospital-based study rather than population based.

1.17% of tuberous sclerosis complex in autistic disorder can be a reliable estimate of the genuine association of autistic disorder and tuberous sclerosis complex in our study. However, as this was a hospital-based study, we might be underestimating the really incidence of tuberous sclerosis complex in autistic disorder, since not all autistic children were routinely examined in order to detect signs for diagnosing TSC. Gillberg reported tuberous sclerosis complex in autism in a population-based study^[8]. This was also reported in other population studies of autistic disorder^[9-11]. In a hospital-based survey of autistic disorder and tuberous sclerosis complex, from the Tuberous Sclerosis Complex Registry in the Hong Kong island, autistic disorder as defined by the *Autistic Disorder Diagnostic Interview-Revised and Diagnostic and Statistical Manual of Mental Disorders-IV*, autistic disorder were defined in 7 children among 44 cases with tuberous sclerosis complex; seven had tuberous sclerosis complex among 753 children with autistic disorder ^[3]. Smalley reported that among autistic populations, the frequency of TSC is 1-4% and perhaps as high as 8-14% among the subgroup of autistic individuals with a seizure disorder ^[12], and Gillberg and Coleman estimated that 9% of children with autistic disorder have tuberous sclerosis complex ^[13].

The prevalence rate of tuberous sclerosis complex in children with autistic disorder in our region was relatively low at 1.17%. Bias between different studies might be introduced depending on whether the researches are cohort or population based. Different authors might come from different subspecialties and have a different background; thus, the age at which these children were diagnosed varies as well^[3]. In addition, study population and number also could produce a considerable bias.

According to our study and other researches, autism spectrum disorder was a condition that might be associated with the development of Tuberous sclerosis complex. The results of a population-based survey among 152,732 Finnish children and adolescents showed that autistic disorder was associated with tuberous sclerosis^[14]. Tuberous sclerosis complex results from mutations in one of two genes, TSC1 and TSC2, coding for hamartin and tuberin, respectively^[15]. Chopra and Lawson reported that there was a trend towards greater severity for patients with TSC2 mutations compared with their TSC1 counterparts, particularly for autistic spectrum disorder, but this did not reach statistical significance^[16]. Can autism spectrum disorder introduce the mutation in the *TSC1* or *TSC2* gene? More work is needed to clarify the mechanisms that underlie this unique association and the variability in expression before one can understand the biologic processes involved in the etiology of both diseases.

This study has a number of limitations. The disparity in the patients' sex (male to female ratio 10:1) could have biased results. It is possible that in our region a boy can obtain parents' more attention. In additional, this was a hospital-based study rather than a population based. It cannot be assumed that they will apply to other centers or

populations. The samples were also geographically limited, potentially limiting the generalizability of our results.

Conclusion

The prevalence rate of tuberous sclerosis complex in autistic disorder in our region was 1.17%. Autism spectrum disorder is a condition that might be associated with the development of Tuberous sclerosis complex. It is unfortunate that we did not have performed genetic analysis for our cohort because this test is not available locally. Furthermore, this survey was just a small cohort study, a large multicenter approach would be necessary to obtain the necessary knowledge.

Acknowledgment

The authors express their great gratitude to all the patients who participated in this study, and to the clinicians involved in this research. This research was officially registered as project No. 08-042 at the China Rehabilitation Research Center. The protocol and informed consent for this study were reviewed and approved by the Institutional Review Board at the China Rehabilitation Research Center

Conflict of Interest: None

References

1. Muhle R, Trentacoste SV, Rapin I. The genetics of autism. *Pediatrics* 2004;113(5):472-86.
2. Daniels AM, Rosenberg RE, Anderson C, et al. Verification of parent-report of child autism spectrum disorder diagnosis to a web-based autism registry. *J Autism Dev Disord* 2012;42(2):257-65.
3. Wong V. Study of the relationship between tuberous sclerosis complex and autistic disorder. *J Child Neurol* 2006;21(3):199-204.
4. Wiznitzer M. Autism and tuberous sclerosis. *J Child Neurol* 2004;19(9):675-9.
5. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th ed-Text Revision (DSMIV-TR). Washington, DC: American Psychiatric Association. 1994.
6. Lord C, Rutter M, Le Couteur A. Autistic Disorder Diagnostic Interview-Revised: A revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *J Autistic Disord Dev Disord* 1994;24(5):659-85.
7. Roach ES, DiMario FJ, Kandt RS, et al. Tuberous Sclerosis Consensus Conference: Recommendations for diagnostic evaluation. *J Child Neurol* 1999; 14:401-7.
8. Gillberg IC, Gillberg C, Ahlsen G. Autistic behaviour and attention deficits in tuberous sclerosis: A population based study. *Dev Med Child Neurol* 1994;36(1):50-6.
9. Hunt A, Shepherd C. A prevalence study of autism disorder in tuberous sclerosis. *J Autistic Disord Dev Disord* 1993;23(2):323-39.
10. Curatolo P, Porfirio MC, Manzi B, Seri S. Autism in tuberous sclerosis. *Eur J Paediatr Neurol* 2004; 8(6):327-32.
11. Wiznitzer M. Autism and tuberous sclerosis. *J Child Neurol* 2004;19(9):675-9.
12. Smalley SL. Autism and tuberous sclerosis. *J Autism Dev Disord* 1998;28(5):407-14.
13. Fombonne E, Du Mazaubrun C, Cans C, Grandjean H. Autism and associated medical disorders in a French epidemiological survey. *J Am Acad Child Adolesc Psychiatry* 1997;36(11):1561-9.
14. Kielinen M, Rantala H, Timonen E, et al. Associated medical disorders and disabilities in children with autistic disorder: a population-based study. *Autism* 2004;8(1):49-60.
15. Riquet A, Cuisset JM, Cuvellier JC, et al. Characteristics of tuberous sclerosis in children. *Arch Pediatr* 2010;17(9):1338-45.
16. Chora M, Lawson JA, Wilson M, et al. An Australian tuberous sclerosis cohort: Are surveillance guidelines being met? *J Paediatr Child Health* 2011;47(10):711-6.